The effects of melatonin the occurence of on post-operative delirium in hip fracture patients a randomized, double-blind, placebo controlled trial

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To assess whether profylactic treatment with 3 mg melatonin daily for 5 days in acutely admitted eldery with hip fractures reduces the incidence of the development of delirium.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Deliria (incl confusion)
Study type	Interventional

Summary

ID

NL-OMON31932

Source
ToetsingOnline

Brief title
MAPLE A

Condition

- Deliria (incl confusion)

Synonym
psychosis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Uit AMC geld tnv dr de

Rooij

Intervention

Keyword: Melatonin profylaxis elderly delirium

Outcome measures

Primary outcome

The differences in the occurrence of delirium within 8 days after hospital admission for surgical repair of hip fracture between patients in the treatment arm and in the control arm.

Secondary outcome

1] Severity and duration of delirium in the treatment and in the control arm.

2] Evaluate differences in subtypes of delirium in the treatment and in the control arm.

3] Evaluate differences in length of hospital stay in the treatment and in the control arm.

4] Compare the additional use of benzodiazepines during delirium in the treatment and in the control arm.

5] Compare the total dose of haloperidol used during delirium in patients the treatment and in the control arm.

6] Evaluate the differences between in-hospital complications in the treatment and in the control arm.

7] Evaluate the differences in cognitive and functional decline at 12 months after hospital discharge between the treatment and in the control arm.

8] Evaluate the differences in mortality during hospital stay and after 12 months follow-up between the treatment and in the control arm.

9] Evaluate differences in DNA profile between delirious and non-delirious patients.

Subgroup:

10] Evaluate differences in the course of melatonin concentrations between delirious and non-delirious patients receiving placebo or melatonin 3 milligram ante noctum.

Study description

Background summary

Delirium is a frequent problem in acutely admitted elderly patients and is associated with increased morbidity and mortality, prolonged hospital stay and with increased economic and emotional costs.
The sleep patterns of patients with delirium are often disturbed, these patients often sleep at day time and showing a fragmented sleep during the night. Although many other risk factors may contribute, the older hospital patient seems to be at significantly increased risk for developing delirium.Though patients usually recover after treating the provocative factor, delirium has a mean duration of 4 days [2-7 days]. Passing delirium is even after hospital discharge associated with a three-times increased mortality risk, higher institutionalisation rate and increased health care costs.
Thus, reducing the duration and severity of delirium and subsequently treatment intensity could benefit patients in many ways and might reduce costs.

Sleep disturbances occur also more often in elderly hospital patients and have been correlated with melatonin9;10. Melatonin, a hormone secreted by the pineal gland and synthesized from serotonin, plays an important role in the regulation of the sleep-wake cycle.11
The circadian rhythm of serum melatonin secretion is influenced by light and is closely synchronized with the habitual hours of sleep. Alterations in synchronization due to unusual working hours or airline flights are correlated with sleep disturbances.
In ICU patients, sleep deprivation and a loss of circadian rhythm have also been associated with melatonin. Additionally, in post-operative ICU patients with delirium an irregular circadian pattern of melatonin secretion has been found. Shigeta et al. showed in elderly patients with a post-operative delirium

different patterns of melatonin secretion suggesting that sleep deprivation trigged delirium.These results all suggest a role between delirium and melatonin.

Recently investigations into the relationship between melatonin therapy and delirium have been undertaken. In 2004 Lewis hypothesized that exogenous administration of melatonin might reduce delirium, as was later on successfully demonstrated in one case report. Melatonin administration also seems to enhance sleep time and night activity in patients with Alzheimer*s dementia where it was administered in a randomized clinical trial showing no adverse effects. Although Alzheimers* disease and delirium have sleep disorders and disturbances in circadian rhythms in common, clinical evidence to confirm the potential benefits of melatonin therapy in treating delirium is currently insufficient. More clinical trials with melatonin therapy may supply with the evidence of potential beneficial effects of suppletion on the course of delirium.

Although there is a high need for preventative measures because of high prevalence, till so far, no drugs have been found preventing postoperative delirium (POD). Haloperidol as a prophylactic drug is not effective in reducing the incidence of POD; it can not prevent delirium in patients admitted for surgical repair after hip fracture.
Additionally, the use of haloperidol in treating delirium is not without risks, as in older patients the presence of delirium often indicates frailty and the presence of many comorbidities. Haloperidol is nevertheless advised as first choice drug in the Dutch CBO guideline Delirium (2005), although the safety of haloperidol on the occurrence of complications, such as a prolonged QT-interval or extra pyramidal symptoms in patients is of concern, especially in older patients with acute illness and a higher frequency of other prescribed medications with a prolongation on the QT-interval.

Study objective

To assess whether profylactic treatment with 3 mg melatonin daily for 5 days in acutely admitted eldery with hip fractures reduces the incidence of the development of delirium.

Study design

Multi-centered, prospective randomized, placebo-controlled trial

Intervention

Patients will receive melatonin 3 milligrams ante noctum for five consecutive days.

Study burden and risks

Burden:
Daily Confusion Assesment Method will take ca. 10 minutes for a minimum of 8 days.
in delirious patients also a DRS and DSI will be taken, this can be done during a normal conversation, within the same 10 minutes
In all patients a bloodsample will be taken on day 3 to asses their DNA profile.
One month and a year after admission, patients will be visited at home to asses their cognitive and functional status by KATZ and MMSE questionnaire; these visits will take approx. 15 minutes.
One year afetr admission the primary caregiver will be asked to fill in the KATZ questionnaire by phone, this will take ca. 5 minutes.
Furthermore, in a subgroup of patients, who have given informed consent separetaly, bloodsamples will be drawn on the first day post-operative and (in case of passed delirium) on the first day of resolution of delirious symptoms. on these days, blood will be drawn on four different times (9.00, 20.00, 22.00 and 2.00).

Some patients may directly benefit from the use of melatonin as profylaxis for developing delirium. Others however will not receive any therapeutic benefit from this study. However, the results may benefit the whole group of eldery patients who are acutely admitted to a hospital. Furthermore patients included in this trial will be closely monitored for the development of delirium and for cognitive impairment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Age 65 yrs or older
Acute hospital admission for hipfracture

Exclusion criteria

No informed consent
No understanding and speaking of dutch language

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-12-2008
Enrollment:	340

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Melatonin
Generic name:	N-Acetyl-5-methoxytryptamine,
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-08-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-04-2009
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-01-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2010
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-000996-57-NL
Other	is applied for
CCMO	NL22814.018.08